UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/652,743 | 08/31/2000 | Mads Norregaard-Madsen | 5665.400-US | 3499 |

25908 7590 07/03/2002

NOVOZYMES NORTH AMERICA, INC.
500 FIFTH AVENUE
SUITE 1600
NEW YORK, NY 10110

| EXAMINER |
|---|
| MOORE, WILLIAM W |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | 11 |

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/652,743 | Applicant(s) NORREGAARD-MADSEN ET AL. | |
|---|---|---|---|
| | Examin r William W. Moore | Art Unit 1652 | |

*-- The MAILING DATE of this communication appears on the cover she t with th correspondence addr ss --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 January 2002 and 12 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,20,32-34 and 40-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40-43* is/are allowed.

6)☒ Claim(s) *1,20,32-34 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,20,32-34 and 40-47* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

*Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claims 1, 20, 32-34 and 40-47 drawn to a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:2, to compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:2, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease, classified, *inter alia*, in class 435, subclass 220.

II. Claims 1, 20, 32-34 and 40-47 drawn to a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:4, to compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:4, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease, classified, *inter alia*, in class 435, subclass 220.

III. Claims 1, 20, 32-34 and 40-47 drawn to a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:6, to compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:6, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease, classified, *inter alia*, in class 435, subclass 220.

IV. Claims 1, 20, 32-34 and 40-47 drawn to a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:8, to compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:8, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease, classified, *inter alia*, in class 435, subclass 220.

V. Claims 1, 20, 32-34 and 40-47 drawn to a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:10, to compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:10, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease, classified, *inter alia*, in class 435, subclass 220.

VI. Claims 1, 20, 32-34 and 40-47 drawn to a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:12, to compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:12, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease, classified, *inter alia*, in class 435, subclass 220.

Inventions of Groups I-VI are unrelated because each comprises a genus of proteases wherein each residual protease, or an altered protease having an amino acid sequence that diverges from a disclosed native protease of any of SEQ IDs NOs: 2, 4, 6, 8, 10, or 12 at as many as 40% of the amino acid sequence positions of the reference protease, is a distinct product having a unique primary structure. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not disclosed to be used together and each will have a different effect relative to the other based upon the primary structure of the particular native residual protease.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Elias Lambiris on May 22, 2002 a provisional election was made with traverse to prosecute the invention of Group VI, a residual protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:12, compositions comprising the protease, to a nucleic acid sequence that encodes a protease sharing at least 60% amino acid sequence identity with the amino acid sequence set forth in SEQ ID NO:12, to vectors host cells comprising the nucleic acid sequence, and to recombinant methods of making the encoded protease of claims 1, 20, 32-34 and 40-47. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1, 20, 32-34 and 40-47 are withdrawn from further consideration by the examiner to the extent they describe a native residual protease having an amino acid sequence set forth in SEQ IDs NOs:2, 4, 6, 8 and 10, or sharing at least 60% amino acid sequence identity with the amino acid sequences set forth in SEQ IDs NOs2, 4, 6, 8 and 10, compositions comprising any of these other proteases, nucleic acid sequences encoding any of these other proteases, vectors host cells comprising these other nucleic acid sequences, and recombinant methods of making these further encoded proteases, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

*Priority*

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copies of both of Applicant's foreign priority documents submitted with Paper No. 6 filed April 24, 2001, the Danish patent applications PA 1999 01212 and PA 1999 01500 filed, respectively, August 31, 1999, and October 20, 1999, have been placed in the file. It is noted that the elected amino acid sequence of SEQ ID NO:12 and its encoding nucleic acid sequence, SEQ ID NO:11, are both disclosed in the earlier priority document.

*Preliminary Amendments*

Applicant's Preliminary Amendments A and B, Papers Nos. 5 and 9 filed on August 31, 2000 and January 22, 2002, respectively, have been entered and claims 2-19, 21-31 and 35-39 were canceled at Applicant's request. Amendment A provides, at page 1, line 1 of the specification, a description of Applicant's claim to priority and Amendment B provides an amended version of the Sequence Listing in printed form.

*Specification*

The disclosure is objected to because of the following informalities: Neither the specification, nor the Preliminary Amendments, include any sequence identifiers, SEQ IDs NOs:2, 4, 6, 8, 10, 12 and 14, in the description of Drawing Figures at page 5, line 24-28, of the specification to indicate which sequence corresponds to an acronym at the top of Figure 1a. Consequently, the specification provides no integral description relating the individual amino acid sequences of Figure 1 with the sources represented by acronyms in Figure 1. Enlarging the Drawing Description of Figure 1 in the specification to relate the acronym therein to a sequence identifier present in the specification's sequence listing, and to further include the other acronyms set forth in Figure 1a together with their sequence identifiers in iterative fashion will cure this deficiency. Appropriate correction is required.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 20, 32-34 and 44-47 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 40-43 are not subject to this rejection because the specification is considered to provide an inherent disclosure of the signal peptide and propeptide regions of the JA96 protease set forth in SEQ ID NO:12, thus also providing an inherent disclosure of all isocoding nucleic acid sequences that encode these two regions. It is agreed that the specification describes, pages 9-15, 23-32 and 77, forty-six different amino acid sequence positions where amino acid substitutions may produce variants of the JA96 protease, but these amount to only 15% of the 302 amino acid positions and the specification discloses preparation of only one paired substitution, page 77, at positions 155 and 156. There is no adequate description of any significant number of the myriad species embraced by claims 1 and 20, however, where these claims permit alterations anywhere within the amino acid sequence of SEQ ID NO:12. Claims 32-34 and 44-47 are included in this rejection because all depend from the independent claims 1 and 20, where claim 1, see, e.g., clause (ii), describes further, undesignated, structural alterations of the native amino acid sequence of a JA96 protease set forth in SEQ ID NO:12, and where claim 20, e.g. clause (a), describes a nucleotide sequence that need not encode a native JA96 protease amino acid sequence set forth in SEQ ID NO:12. Similarly, the specification fails to identify any native epitopes of SEQ ID NO:12, nor any epitopes that might result from the several specific modifications it discloses; neither does it exemplify or describe the

design or preparation of divergent JA96 proteases that share no more than a common epitope with an undisclosed epitope of SEQ ID NO:12 according to clause (i) of the claim. Indeed, there is no indication anywhere in the specification that any antibody had been raised to even the native JA96 protease at the time Applicant's priority document was filed or that Applicant made or deposited an antibody-producing cell line. The specification further fails to exemplify or describe the preparation of subject matters of claim 1 which are the myriad products with amino acid sequences that diverge as much as 40% from the mature residual protease set forth in SEQ ID NO:12 according to clause (ii) therein or the preparation of the subject matters of claim 20 which are the myriad nucleic acid sequences that might encode amino acid sequences that diverge as much as 40% from the mature residual protease set forth in SEQ ID NO:12.

Neither can the specification be considered to provide an adequate written description of inventions according to clauses (iiia) or (iiib) of claim 1 where it fails to show that any nucleic acid sequence hybridizations were performed with any region of SEQ ID NO:11 – or with a sequence isocoding with any region of SEQ ID NO:11 – to identify, isolate or prepare nucleic acid sequences encoding proteases altered at further amino acid sequence locations. Likewise, the specification does not show that any allelic variants of the *B. pumilis* protease of SEQ ID NO:12 were identified or isolated according to the terminal clause of claim 1, nor that any "subsequence" of undisclosed products of the terminal clause of claim 1 was ever prepared that may have protease activity. The specification does not otherwise disclose or suggest the nature or source of any of any generic proteins that meet limitations of the various clauses of the claim. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601,

1605 (Fed. Cir. 1993). The specification furnishes relevant identifying characteristics of only certain, specific, modifications of the amino acid sequence of SEQ ID NO:12 but does not otherwise indicate that Applicant designed or prepared proteases having more than two concurrent alterations nor does Applicant provide any other characteristic permitting a correlation between the undisclosed structures of any protein among the myriad species of undefined, generic, proteins of clauses (i)-(iiib) of claim 1 and the disclosed amino acid sequence of SEQ ID NO:12.

The Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, proteases of other microbial species, with no indication that Applicant had either made or identified them, such as that of Rebrikov et al., made of record herewith. Nothing demonstrates that Applicant, at the time the specification was filed, was "able to envision" enough of the structure of any undisclosed generic protein to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). Other than the disclosed JA96 variants, the specification's treatment of subject matters of clauses (i)-(iiib) of claim 1, or its terminal clause, and of subject matters of clauses (a)-(e) of claim 20, is considered to be entirely prospective where skilled artisans in the relevant fields of molecular biology and protein engineering could not predict the structure, or other properties, of the claimed products.

Claims 1, 20, 32-34 and 44-47 are further rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a residual protease either having the amino acid sequence set forth in SEQ ID NO:12, or having an amino acid sequence comprising one or more amino acid substitutions selected from the group of JA96 protease substitutions set forth at pages 25-32 of the specification, for compositions comprising said proteases, and for nucleic acid sequences encoding such proteases, vectors and host cells comprising said nucleic acid sequences, and for recombinant methods of making the encoded proteases utilizing such vectors and host cells,

does not reasonably provide enablement for a protease having an amino acid sequence that diverges from that of SEQ ID NO:12 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 40% of the amino acid positions within the mature residual protease of SEQ ID NO:12, or compositions comprising same, or nucleic acid sequences encoding same, vectors and host cells comprising said nucleic acid sequences, or for recombinant methods of making the encoded proteases utilizing such vectors and host cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 40-43 are not subject to this rejection because the skilled artisan would require no undue experimentation to determine both the signal peptide and propeptide regions of the JA96 protease set forth in SEQ ID NO:12, nor require any experimentation at all for prepare all isocoding nucleic acid sequences that encode these two regions, as well as expression vectors and host cells that comprise such coding sequences fused to a nucleic acid sequence encoding a heterologous polypeptide, or to practice the recombinant method of producing the encoded fusion polypeptide of claim 43. Claims 1, 20, 32-34 and 44-47 are rejected herein because the specification fails to enable the subject matters described by at least the clauses of claims 1 and 20 that at least have the most defined scope of either claim: clause (ii) of claim 1, and the corresponding clause (a) of claim 20. Claims 1 and 20, and claims 32-34 and 44-47 dependent thereon, are rejected where they contemplate arbitrary assignments of any or all of amino acid substitutions, additions or deletions in a protease of SEQ ID NO:12 at as many as 40% of the amino acid positions in its primary structure. Construing "homology" conservatively, as a one-to-one positional identity or non-identity, still allows these claims to reach proteases that diverge at as many as 120 amino acid positions among the 302 amino acids of the JA96 protease having the amino acid sequence set forth in SEQ ID NO:12 and nucleic acid sequences

that encode these variants. The teachings of the specification are inadequate to support introduction of as many as 120 amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the mature JA96 protease amino acid sequence set forth in SEQ ID NO:12.

While the single and paired amino acid sequence substitutions at positions taught by the specification are straightforward and may be combined, neither the prior art made of record herewith nor the specification can, even if taken together, identify any and all conceivable sets of concurrent 120 modifications in the amino acid sequence of the JA96 protease of SEQ ID NO:12 that might be altered, nor teach the nature of the alterations that might be made, which will permit a resulting polypeptide to function as a protease. The prior art made of record herewith is evidence that no teaching in the relevant arts of protein engineering and molecular biology can be combined with the disclosure of the instant specification to support such extensive alteration. Mere sequence perturbation will not enable the design and preparation of nucleotide sequences encoding a myriad of divergent proteases and provide the public with a nucleotide sequence encoding a protease that retains its native function. It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement).

The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable

correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the JA96 protease of SEQ ID NO:12 to the extent claims 1 and 20 permit,

b) the specification lacks working examples wherein the mature JA96 protease of SEQ ID NO:2 is altered to the extent permitted by claims 1 and 20,

c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no members of the class of residual proteases represented by the amino acid sequence of the JA69 protease of SEQ ID NO:12 have had as many as 120 amino acids specifically identified for concurrent modification.

Thus the scope of the claimed subject matters embraced by the phrase, "at least 60% homologous thereto", is considered to be unsupported by the present specification, even when taken in combination with the teachings available in the prior art.

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 20 and 32-34 are rejected under 35 U.S.C. §102(a) as being anticipated by Rebrikov et al., 1999, ***Journal of Protein Science***, Vol. 18, pages 21-25, made of record herewith.

Rebrikov et al. disclose, Figure 2, the amino acid sequence and encoding nucleic acid sequence of a *Bacillus* glutamyl endopeptidase of the trypsin family of serine proteases that is capable of cleaving at glutamates within polypeptides and that shares 96.3% amino acid sequence identity with the JA96 amino acid sequence of SEQ ID NO:12 herein, diverging at but three amino acid positions within the protease domain, thus meeting the limitations of claims 1 and 20 herein. Rebrikov et al. teach that the protease is active in hydrolyzing casein, Figure 1 and page 22. None of claims 32-34 herein require any particular set of translational or transcriptional regulatory nucleic acid sequences, any particular vector, or a particular host cell, thus the further teaching of Rebrikov et al., page 22 left column, of inserting an isolated *B. intermedius* DNA comprising the protease-encoding nucleic acid sequence together with its native expression signals into a plasmid vector suitable for expression of a heterologous polypeptide in a *Bacillus* host cell, and of transforming a *Bacillus subtilis* host cell with the plasmid in order to recombinantly express the protease to assay its proteolytic activity, meets the limitations of claims 32-34 herein. The disclosure Rebrikov et al. fails to meet limitations of claim 40 herein, and cannot be combined with other prior art teachings, such as Dambmann et al., U.S. 5,866,357, made of record

herewith, and Estell et al., EP 0 251 446, made of record with Applicant's Information Disclosure Statement, to meet limitations of claim 40, because the protease signal peptide and propeptide regions of their *B. intermedius* glutamyl endopeptidase together differ at nine amino acid positions from corresponding regions of SEQ ID NO: 12 where claim 40 requires that a nucleic acid sequence encode these regions of SEQ ID NO: 12.

*Allowable Subject Matter*

Claims 40-43 are free of the prior art for the reasons set forth above and are allowed herewith. Apart from the protease of Rebrikov et al., a glutamyl endopeptidase disclosed by both Teraoka et al., **EP 0 482 879**, made of record with Applicant's Information Disclosure Statement, and Kakudo et al., 1992, **The Journal of Biological Chemistry**, Vol. 267, pages 23782-23788, made of record herewith, has the closest structural relationship to the JA96 protease of SEQ ID NO:12, but cannot meet limitations of claims 1 and 20 where it shares only 27% amino acid sequence identity with the sequence set forth in SEQ ID NO:12. Each of the patents to Budtz et al., **U.S. 5,523,237**, Dambmann et al., **U.S. 5,863,573**, and Dambmann et al., **U.S. 5,866,357**, made of record herewith, disclose the same protease, sharing but 26% amino acid sequence identity with the JA96 sequence set forth in SEQ ID NO:12. Amending claims 1 and 20 herein to overcome rejections under the first paragraph of 35 U.S.C. §112 above by limiting them to the amino acid sequence set forth in SEQ ID NO:12, or a specific variant disclosed herein, would permit their allowance where such amended subject matter would be free of the prior art of record which suggests neither the specific amino acid sequence of SEQ ID NO:12 nor any of the specific variants of SEQ ID NO:12 disclosed herein.

Amending claims 1 and 20 herein to overcome rejections under the first paragraph of 35 U.S.C. §112 above by limiting them to the amino acid sequence set forth in SEQ ID NO:12, or a specific variant disclosed herein, would also permit the allowance of claims

44-47. The prior art of record cannot be combined with teachings of Rebrikov et al. to render these claims obvious where the closest prior art, Teraoka et al., Budtz et al., and the patents to Dambmann et al., generally teach that, unlike members of the subtilisin family of serine proteases, microbial proteases of the trypsin family of serine proteases that specifically cleave adjacent to glutamates in polypeptides should either be eliminated from the spectrum of proteases expressed by their native source by deleting or disrupting their encoding genes or, if retained, should be used in compositions for processing protein, such as those disclosed in the patents to Dambmann et al. Thus the prior art teaches away from using either the protease of Rebrikov et al. or the protease of SEQ ID NO:12 in detergent compositions of claims 44-47 and further teaches away from making the prior art amino acid modifications in SEQ ID NO:12 described at pages 23-32 of the specification customarily used to improve the endoproteolytic activity of members of the subtilisin family of serine proteases in detergent compositions taught, e.g., by Bott et al., Wells et al.. and Sierkstra et al. made of record with Applicant's Information Disclosure Statement.

*Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. The examiner's direct FAX telephone number is 703.746.3169. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
June 26, 2002

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600